Lifestyle, Inflammation, and Vascular Calcification in Kidney Transplant Recipients

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Dutch Summary

Na decennia van verbeteringen in chirurgische technieken, immunosuppressieve medicatie, behandeling van afstoting, behandeling van infectieziekten en preventie van complicaties, is niertransplantatie tegenwoordig de behandeling van keuze bij patiënten met eindstadium nierfalen. Niettemin blijft er veel ruimte voor verbetering. Twee van de grote problemen die nog steeds in dit veld bestaan zijn een sterk verhoogd risico op hart- en vaatziekten na niertransplantatie en het frequent optreden van laat falen van de getransplanteerde nier, waarbij dit laatste leidt tot de noodzaak van terugkeer naar dialyse of een hernieuwde niertransplantatie. Voor dit proefschrift hebben we verschillende traditionele en nieuwe, potentieel modificeerbare risicofactoren bij niertransplantatiepatiënten onderzocht om te kijken of we hierbij mogelijke verbeterpunten zouden kunnen identificeren waar tot nu toe wellicht overheen gekeken is en die uiteindelijk zouden kunnen leiden tot nieuwe behandelingsmogelijkheden om de ziektelast en de maatschappelijk last die gepaard gaan met hart- en vaatziekten en het ontstaan van falen van de getransplanteerde nier bij niertransplantatiepatiënten te verminderen.

Deel I — Levensstijl, gezond dieet en schadelijke bestanddelen

In **hoofdstuk 2** beschrijven we onze bevinding dat een relatief hoge groente consumptie bij niertransplantatiepatiënten sterk is geassocieerd met een lager risico op voortijdig overlijden, vooral overlijden door hart- en vaatziekten. Tot op heden is er geen duidelijke klinische reden om de consumptie van fruit en groente waar bij niertransplantatiepatiënten aan te moedigen, terwijl er door dieetmaatregelen uit het verleden juist vaak sprake is van een relatief lage consumptie. Wij dragen met ons onderzoek de eerste aanwijzingen aan om een hogere inname van fruit en groente bij niertransplantatiepatiënten aan te moedigen. In **hoofdstuk 3** beschrijven wij onze bevinding van een inverse associatie tussen uit een zoutwater milieu afkomstige omega 3 meervoudige onverzadigde vetzuren en vis intake met voortijdig overlijden aan hart- en vaatziekten bij niertransplantatiepatiënten. Ons gegevens laten zien dat de visinname van Nederlandse niertransplantatiepatiënten relatief laag is, hetgeen suggereert dat er ruimte voor verbetering is om het optreden van hart- en vaatziekten bij niertransplantatiepatiënten te verminderen. We vonden geen aanwijzingen dat het positieve effect dat uitging van visinname werd tegengegaan door de hogere kwikconcentraties in het bloed waarmee een hogere

visintake gepaard bleek te gaan. Al met al onderschrijven deze bevindingen het feit dat meer onderzoek naar individuele aanbevelingen voor verhoging van fruit, groente en visinname bij niertransplantatiepatiënten is aangewezen en kansrijk is om de gezondheidstoestand van niertransplantatiepatiënten te verbeteren.

Behalve vis en de vervuiling ermee met kwik, is cadmium een belangrijke aan de leefomgeving en leefstijl gerelateerde schadelijke stof, waarvan blootstelling eraan vooral schadelijk kan zijn voor niertransplantatiepatiënten. In **hoofdstuk 4** beschrijven wij onze bevinding dat laaggradige blootstelling aan cadmium gepaard gaat met een tot nu toe niet eerder onderkend risico op voortijdig verlies van functie van de getransplanteerde nier, waarbij de verhoging van het risico zich al afspeelt in de range van concentraties die tot nu toe als normaal beschouwd wordt. Dit geeft aan dat lichamelijke blootstelling aan cadmium van klinische belang kan zijn, een aanleiding zou kunnen zijn tot vermijding van blootstelling, vaststelling van niveau van blootstelling en eventueel behandeling. Monitoring van cadmium concentraties en behandeling om niveaus van cadmium te verlagen zou een nieuwe en tot nu toe ongedachte manier kunnen zijn om het ontstaan van laat transplantaatfalen te verminderen.

Deel II — Ontsteking, oxidatieve stress en vaatverkalking

In **hoofdstuk 5** beschrijven wij onze bevinding dat lage plasma vitamine C concentraties die passen bij depletie bij niertransplantatie vaak (22%) voorkomen en dat dergelijke lage concentraties onafhankelijk zijn geassocieerd met een verhoogd risico op voortijdig overlijden. We vonden daarnaast dat een samengestelde score van vooraf bepaalde ontstekings-gerelateerde biomarkers ongeveer een derde deel van deze associatie verklaarde, hetgeen suggereert dat het gunstige effect van vitamine C bij niertransplantatiepatiënten voor een aanzienlijk deel loopt via vermindering van chronische laaggradige inflammatie. Terwijl de dagelijks aanbevolen hoeveelheid van vitamine C inname (40 mg per dag voor volwassenen) in principe gehaald kan worden via een gezond dieet, lijkt het ook interessant om in studieverband na te gaan of er verbetering kan worden bewerkstelligd via toediening van grotere hoeveelheden vitamine C dan uit een gezond dieet verkregen kan worden.

In **hoofdstuk 6** beschrijven wij onze bevinding dat een toename van de biomarkers Carboxymethyllysine en Carboxyethyllysine gepaard gaat met een toename van het risico op voortijdig overlijden aan hart- en vaatziekten bij

niertransplantatiepatiënten. Vrije thiol groepen en de oplosbare vorm van het zogenaamde “vascular cell adhesion molecule-1” verklaarden gezamenlijk ongeveer 35% van deze verbanden, hetgeen ondersteunt dat oxidatieve stress, ontsteking en endotheeldysfunctie bijdragen aan het verhoogde risico op hart- en vaatziekten bij niertransplantatiepatiënten.

In **hoofdstuk 7** beschrijven wij onze studie over galectine-3, hetgeen als β-galactoside bindend lectine een nieuwe biomarker is voor de neiging tot het vervangen van normaal weefsel door bindweefsel. We vonden dat circulerende concentraties van galectine-3 erg hoog zijn bij niertransplantatiepatiënten en we vonden ook dat deze concentraties onafhankelijk zijn geassocieerd met een verhoogd risico op het ontstaan van transplantaatfalen tijdens een periode van ongeveer 10 jaar aan follow-up. Hierbij was de associatie vooral sterk bij niertransplantatiepatiënten die rookten en zij die een verhoogde systolische bloeddruk hadden.

Het verhoogde cardiovasculaire risico bij niertransplantatiepatiënten zou deels kunnen afhangen van een verschuiving van de neiging van verkalking van de botten naar verkalking van zachte weefsels, met aan de ene kant botontkalking en aan de andere kant vaatverkalking als gevolg. In **hoofdstuk 8** beschrijven wij onze bevinding dat een lage botdichtheid zoals gemeten middels de zogenaamde “Dual-Energy X-ray Absorptiometry” (DEXA) techniek in hoge frequentie (54%) voorkomt bij niertransplantatiepatiënten en dat een lage botdichtheid onafhankelijk is geassocieerd met een verhoogd risico op verkalking van de grote lichaamsslagader in de buik, waarmee we verdere steun lenen aan de hypothese dat sprake is van een zogenaamde “bot-vaat as” bij niertransplantatiepatiënten. Omdat DEXA scans niet invasief en relatief accuraat zijn ondersteunen deze resultaten de gedachte dat dergelijke scans naast hun gebruikelijk rol als screening voor botontkalking ook gebruikt kunnen worden als screening voor vaatverkalking, hetgeen kan helpen om tegelijkertijd richting te geven aan de behandeling van botontkalking en de behandeling van hart- en vaatziekten bij niertransplantatiepatiënten.

Spanish Summary

Luego de décadas de mejoras en las técnicas quirúrgicas, prevención de complicaciones, tratamiento del rechazo y enfermedades infecciosas, el trasplante de riñón es ahora el tratamiento de elección para los pacientes con enfermedad renal crónica. Sin embargo, aún queda mucho por mejorar en el cuidado a largo plazo de pacientes receptores de trasplante renal (RTR) ambulatorios. Alto riesgo de enfermedad cardiovascular y falla tardía del injerto con indicación de diálisis o nuevo trasplante, son dos de los grandes problemas de estos pacientes. En esta tesis investigamos varios factores de riesgo potencialmente modificables, apuntando a novedosas oportunidades de manejo del riesgo a largo plazo de eventos adversos, proporcionando una base para el desarrollo de nuevos enfoques de intervención para disminuir la carga de enfermedad cardiovascular y falla tardía del injerto en RTR ambulatorios.

Parte I — Estilo de vida; Dieta saludable y Contaminantes Tóxicos

Hasta la fecha no existe un incentivo clínico claro para prescribir la liberación del consumo de frutas y verduras post-trasplante renal. En el **capítulo 2** mostramos que un aumento en el consumo de vegetales está fuertemente asociado con un menor riesgo de mortalidad general y cardiovascular en RTR. Proporcionamos la primera evidencia para avanzar hacia el desarrollo de recomendaciones clínicas orientadas a obtener un beneficio de supervivencia como consecuencia del aumento relativo del consumo de frutas y verduras en RTR ambulatorios. En el **capítulo 3** describimos una asociación inversa entre la ingesta de pescado o la ingesta de ácidos grasos poliinsaturados omega-3 de origen marino y el riesgo de mortalidad cardiovascular en RTR. Nuestros hallazgos también sugieren que la ingesta de pescado en pacientes holandeses es relativamente baja, señalando una potencial estrategia para reducir el riesgo de mortalidad cardiovascular en dichos pacientes. Para la asociación entre ingesta de pescado y riesgo de mortalidad, no encontramos evidencia clara de un potencial efecto contrarrestante derivado del consumo concomitante de mercurio. En general, estos hallazgos subrayan la necesidad de corroborar y complementar el estudio de nuevas estrategias de intervención basadas en recomendaciones individualizadas para aumentar la ingesta de frutas, verduras y pescado que pueden disminuir la carga de eventos adversos en RTR.

Más allá de la contaminación por mercurio en pescados y mariscos, el cadmio es otro contaminante tóxico ambiental relacionado con el estilo de vida que, en teoría, puede ser particularmente peligroso para RTR. En el

capítulo 4 describimos que la exposición a cadmio representa un peligro hasta ahora relativamente subestimado para conservar el funcionamiento del injerto renal a largo plazo. Observamos que, incluso desde pequeños niveles plasmáticos hasta niveles relativamente altos, pero generalmente considerados normales, cadmio se asocia con mayor riesgo de falla tardía del injerto en RTR. Monitorización ambulatoria de cadmio y enfoques de intervención dirigidos al cadmio pueden representar novedosas estrategias de manejo para reducir significativamente el riesgo de falla tardía del injerto renal.

Parte II — Inflamación y Estrés Oxidativo, y Calcificación Vascular

En el **capítulo 5**, describimos que la depleción plasmática de vitamina C en RTR ambulatorios es relativamente común (22%) y se asocia de forma independiente con un riesgo de mortalidad casi dos veces mayor. Un conjunto de biomarcadores inflamatorios predefinidos medió aproximadamente un tercio de la asociación entre vitamina C plasmática y riesgo de mortalidad, respaldando la noción de que el efecto beneficioso de la vitamina C sobre la supervivencia de los pacientes se produce, al menos en un grado considerable, a través de la disminución de la inflamación crónica. Si bien la ingesta sugerida de vitamina C (40 mg/d para adultos) se puede obtener a partir de una dieta saludable, estos hallazgos justifican también futuras investigaciones destinadas a explorar potenciales intervenciones farmacológicas en RTR.

En el **capítulo 6** mostramos que el incremento relativo en 1 desviación estándar de los biomarcadores Nε-(carboximetil)lisina y Nε-(carboxietil) lisina se asocia con un aumento clínicamente significativo (~50%) de riesgo de mortalidad cardiovascular en RTR. Los grupos tiol libres y la molécula de adhesión de células vasculares soluble 1 mediaron aproximadamente 35% de estas asociaciones, respaldando la noción de que la inflamación y la disfunción endotelial contribuyen al riesgo cardiovascular aumentado en RTR ambulatorios.

En el **capítulo 7** describimos nuestro estudio sobre la galectina-3, que es un nuevo biomarcador de fibrosis renal. Observamos que los niveles de galectina-3 son notablemente altos en RTR. En nuestra cohorte de RTR, galectina-3 se asoció de forma independiente con un mayor riesgo de falla del injerto durante aproximadamente 10 años de seguimiento, con asociaciones particularmente fuertes en RTR fumadores y con presión arterial sistólica alta.

El aumento del riesgo cardiovascular en RTR depende en parte de un

cambio en la tendencia de calcificación de los huesos hacia los tejidos blandos, incluidos los vasos sanguíneos. En el **capítulo 8** describimos que una baja densidad mineral ósea, según absorciometría de rayos X de doble energía, es altamente prevalente en RTR (54%), y se asocia independientemente con un mayor riesgo de calcificación de la aorta abdominal, entregando evidencia de que soporta la existencia del eje óseo-vascular por primera vez en RTR. Debido a que la absorciometría de rayos X de doble energía no es invasiva y es relativamente acuciosa, estos resultados destacan la noción de que la absorciometría de rayos X de doble energía es un método clínico de imagen útil para la evaluación de masa ósea y calcificación vascular en RTR, lo que puede ayudar en la orientación del manejo terapéutico de la enfermedad ósea y cardiovascular en RTR ambulatorios.

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Camilo

About the Author

Camilo G. Sotomayor was born in Linares, Región del Maule, Chile, on January 18th in 1993. In December 2010, he finished his secondary school education at Colegio Concepción Parral, wherein he had been acknowledged best colleague by his peers, appointed captain of the volleyball team, and chosen president of the student council.

In March 2011, he started Medical School at the University of Chile. Early during his studies, Camilo gained interested in the field of Oxidative Stress and Inflammation, which encouraged him to apply for a position as mentee of Prof. Ramón Rodrigo at the Laboratory of Nephrology and Nephrotoxicity of the Institute of Biomedical Sciences, University of Chile. Herein, he gained 3 years of international research experience, which led him to apply for an Erasmus + Scholarship to undergo an extended and eventually fruitful research training under the supervision of Prof. Stephan J.L. Bakker at the Division of Nephrology of the University Medical Center Groningen, Groningen, The Netherlands.

Before returning to Chile from The Netherlands, Camilo was granted a position as clinical intern at Harvard Medical School's affiliated hospitals, wherein he was graded Honors with Distinction at the Radiology Department of the Boston Children's Hospital. At his return in Chile, he finished his final year of medical school, while continuing research collaboration with Prof. Bakker, with whom he then applied for a CONICYT (*Comisión Nacional de Investigación Científica y Tecnológica*) grant to perform his PhD fellowship back in The Netherlands. There, he had the opportunity to contribute with coordination, data collection, and data management of the TransplantLines-Coronary Artery Calcification study, guide master students with their research internship and publishing activities, and deliver several oral and poster presentations at international conferences over 4 different continents.

After completing his PhD studies, Camilo will continue his research and clinical career performing as post-doctoral researcher and radiology resident at the Clinical Hospital University of Chile, University of Chile, Santiago, Chile.

List of Publications

1. Gormaz JG, Valls N, **Sotomayor CG**, Turner T, Rodrigo R. Potential role of polyphenols in the prevention of cardiovascular diseases: Molecular bases.

Curr Med Chem 2016, 23, 115─128.

2. **Sotomayor CG**, Cortés I, Gormaz JG, Vera S, Libuy M, Valls N, Rodrigo R. Role of oxidative stress in renal transplantation: Bases for an n-3 PUFA strategy against delayed graft function.

Curr Med Chem 2017, 24, 1469─1485.

3. Gomes-Neto AW†, **Sotomayor CG†**, Pranger IG, van den Berg E, Gans ROB, Soedamah-Muthu S, Navis GJ, Bakker SJL. Intake of marine-derived omega-3 polyunsaturated fatty acids and mortality in renal transplant recipients. †These authors contributed equally to this work.

Nutrients 2017, 9, 363.

4. **Sotomayor CG**, Eisenga MF, Gomes-Neto AW, Ozyilmaz A, Gans ROB, de Jong WHA, Zelle DM, Berger SP, Gaillard AJM, Navis GJ, Bakker SJL. Vitamin C depletion and all-cause mortality in renal transplant recipients.

Nutrients 2017, 9, 568.

5. **Sotomayor CG**, Gomes-Neto AW, Gans ROB, de Borst MH, Berger SP, Rodrigo R, Navis GJ, Touw DJ, Bakker SJL. Fish intake, circulating mercury and mortality in renal transplant recipients

Nutrients 2018, 10, 1419.

6. Barrientos R, Samtani S, Frelinghuysen M, **Sotomayor CG**, Gormaz JG, Burotto M. Clinical decision making in postmastectomy radiotherapy in node negative breast cancer.

Ecancermedicalscience 2018, 12, 874.

7. Yepes-Calderón M, **Sotomayor CG**, Gomes-Neto AW, Gans ROB, Berger SP, Rimbach G, Esatbeyoglu T, Rodrigo R, Geleijnse JM, Navis GJ, Bakker SJL. Plasma malondialdehyde and risk of new-onset diabetes after transplantation in renal transplant recipients: A prospective cohort study.

J Clin Med 2019, 8, 453.

8. Fernández-Gajardo R, Matamala JM, Gutiérrez R, Lozano P, Cortés-Fuentes IA, **Sotomayor CG**, Bustamante G, Pasten JA, Vargas G, Guerrero R, Reyes P, Cavada G, Feuerhake W, Rodrigo R. Relationship between infarct size and serum uric acid levels during the acute phase of stroke.

PLoS One 2019, 14, 0219402.

9. Gomes-Neto AW, Osté MCJ, **Sotomayor CG**, van den Berg E, Geleijnse JM, Gans ROB, Bakker SJL, Navis GJ. Fruit and vegetable intake and risk of posttransplantation diabetes in renal transplant recipients.

Diabetes Care 2019, 42, 1645─1652.

10. **Sotomayor CG**, Gomes-Neto AW, van Londen, Gans ROB, Nolte IM, Berger SP, Navis GJ, Rodrigo R, Leuvenink HGD, Schalwijk CG, Bakker SJL. Circulating advanced glycation endproducts and long-term risk of cardiovascular mortality in kidney transplant recipients.

Clin J Am Soc Nephrol 2019, 14, 1512─1520.

11. Yepes-Calderón M, **Sotomayor CG**, Kretzler M, Gans ROB, Berger SP, Navis GJ, Ju W, Bakker SJL. Urinary epidermal growth factor/creatinine ratio and graft failure in renal transplant recipients: a prospective cohort study.

J Clin Med 2019, 8, 1673.

12. Gactiúa A, **Sotomayor CG**, Groothof D, Eisenga MF, Pol RA, de Borst MH, Gans ROB, Berger SP, Rodrigo R, Navis GJ, Bakker SJL. Plasma vitamin C and cancer mortality in kidney transplant recipients.

J Clin Med 2019, 8, 2064.

13. **Sotomayor CG**, Rodrigo R, Gomes-Neto AW, Gormaz GJ, Minovic I, Eggersdorfer ML, Vos M, Riphagen IJ, de Borst MH, Nolte IM, Berger SP, Navis GJ, Bakker SJL. Plasma versus erythrocyte vitamin E in renal transplant recipients, and duality of tocopherol species.

Nutrients 2019, 11, 2821.

14. Tubben A, **Sotomayor CG**, Post A, Minovic I, Frelink T, de Borst MH, Said MY, Douwes RM, van den Berg E, Rodrigo R, Berger SP, Navis GJ, Bakker SJL. Urinary oxalate excretion and long-term outcomes in kidney transplant recipients.

J Clin Med 2019, 8, 2104.

15. Gomes-Neto AW, Osté MCJ, **Sotomayor CG**, van den Berg E, Geleijnse JM, Berger SP, Gans ROB, Bakker SJL, Navis GJ. Mediterranean style diet and kidney function loss in kidney transplant recipients.

Clin J Am Soc Nephrol 2020, 15, 238–246.

16. **Sotomayor CG**, Gomes-Neto AW, Eisenga MF, Nolte IM, Anderson JLC, de Borst MH, Osté MCJ, Rodrigo R, Gans ROB, Berger SP, Navis GJ, Bakker SJL. Consumption of fruits and vegetables and cardiovascular mortality in renal transplant recipients: A prospective cohort study.

Nephrol Dial Transplant 2020, 35, 357–365.

17. **Sotomayor CG**, Groothof D, Vodegel JJ, Gacitúa TA, Gomes-Neto AW, Osté MCJ, Pol RA, Ferreccio C, Berger SP, Chong G, Slart RHJA, Rodrigo R, Navis GJ, Touw DJ, Bakker SJL. Circulating arsenic is associated with long-term risk of graft failure in kidney transplant recipients: A prospective cohort study.

J Clin Med 2020, 9, 417.

18. Carrasco R, Ramírez MC, Nes K, Schuster A, Aguayo R, Morales M, Ramos C, Hasson D, **Sotomayor CG**, Henríquez P, Cortés I, Erazo M, Salas C, Gormaz JG. Prevention of doxorubicin-induced cardiotoxicity by pharmacological non-hypoxic myocardial preconditioning based on docosahexaenoic acid (DHA) and carvedilol direct antioxidant effects: Study protocol for a pilot, randomized, double-blind, controlled trial (CarDHA Trial).

Trials 2020, 21, 137.

19. **Sotomayor CG**, Minović I, Eggersdorfer ML, Riphagen IJ, de Borst MH, Dekker LH, Nolte IM, Frank J, van Zon SKR, Reijneveld SA, van der Molen JC, Vos MJ, Kootstra-Ros JE, Rodrigo R, Kema IP, Navis GJ, Bakker SJL. Duality of tocopherol isoforms and novel associations with vitamins involved in one-carbon metabolism: Results from an elderly sample of the LifeLines Cohort Study.

Nutrients 2020, 12, 580.

20. Yepes-Calderón M†, **Sotomayor CG†**, Gans ROB, Berger SP, Leuvenink HGD, Tsikas D, Rodrigo R, Navis GJ, Bakker SJL. Post-transplantation plasma malondialdehyde is associated with cardiovascular mortality in renal transplant recipients: A prospective cohort study. †These authors contributed equally to this work.

Nephrol Dial Transplant 2020, 35, 512─519.

21. **Sotomayor CG**, te Velde-Keyzer CA, de Borst MH, Navis GJ, Bakker SJL. Lifestyle, inflammation, and vascular calcification in kidney transplant recipients: perspectives on long-term outcomes.

J Clin Med 2020, 9, 1911.

22. **Sotomayor CG†**, Benjamens S†, Gomes-Neto AW, Pol RA, Groothof D, Te Velde-Keyzer CA, Chong G, Glaudemans AWJM, Berger SP, Bakker SJL, Slart RHJA. Bone mineral density and aortic calcification: Evidence for a bone-vascular axis after kidney transplantation. †These authors contributed equally to this work.

Transplantation - Accepted.

23. Van de Kuit A, Benjamens S, **Sotomayor CG**, Rijkse E, Berger SP, Moers C, Bakker SJL, Minnee RC, Yakar D, Pol RA. Postoperative ultrasound in kidney transplant recipients: Association between intrarenal resistance index and cardiovascular events.

Transplantation Direct - Accepted.

24. **Sotomayor CG**, te Velde-Keyzer CA, Diepstra A, van Londen M, Pol RA, Post, A, Gans ROB, Nolte IM, Slart RHJA, de Borst MH, Berger SP, Rodrigo R, Navis GJ, de Boer R, Bakker SJL. Galectin-3 and risk of late graft failure in kidney transplant recipients: A 10-years prospective cohort study.

Transplantation - Accepted.

25. Yepes-Calderón M†, **Sotomayor CG**†, Rasmussen DGK, Hijmans RS, te Velde-Keyzer CA, van Londen M, van Dijk M, Diepstra A, Berger SP, Karsdal AM, Belmelman FJ, de Feijter JW, Kers J, Florquin S, Genovese F, Bakker SJL, Sanders J-S, van den Born J. Biopsy-controlled non-invasive quantification of collagen type VI in kidney transplant recipients: A post-hoc analysis of the MECANO trial. †These authors contributed equally to this work.

J Clin Med - Accepted.

26. Yepes-Calderón M, **Sotomayor CG**, Pena M, Eisenga MF, Gans ROB, Berger SP, Moers C, Sugaya T, Doekharan D, Navis GJ, van den Born J, Bakker SJL. Urinary liver-type fatty-acid binding protein is independently associated with graft failure in outpatient kidney transplant recipients.

Am J Transplant - Accepted.

27. **Sotomayor CG**, Groothof D, Vodegel JJ, Eisenga MF, Knobbe TJ, IJmker J, Lammerts RGM, de Borst MH, Berger SP, Nolte IM, Rodrigo R, Slart RHJA, Navis GJ, Touw DJ, Bakker SJL. Plasma cadmium is associated with increased risk of long-term kidney graft failure.

Kidney Int - Accepted.